Eisai Co., Ltd.

Revised: April 2005 (4th version, Revisions associated with the amendment of the Pharmaceutical Affairs Law)

Standard Commodity Classification No. of Japan
873136

- Drug for peripheral neuropathies -

Methycobal® injection 500 μg

<Mecobalamin preparation>

Prescription drug

Storage
METHYCOBAL should be stored in LPE pack (Light Protect Easy open pack) at room temperature. (If ampules are not kept in the LPE pack, mecobalamin decomposes by light and decreases the content).

Expiration date
METHYCOBAL should be used before the expiration date indicated on the package or label.

Approval No.	57AM-1221
Date of listing in the NHI reimbursement price	Jun 1984
Date of initial marketing in Japan	Jun 1984
Date of latest reexamination	Mar 1998
Date of latest approval of indications	Jul 1983

Caution: See "PRECAUTION FOR HANDLING" section.

Caution : Use only as directed by a physician.

DESCRIPTION

METHYCOBAL is a clear, red injection containing the following ingredients, and contained in brown ample (one-point-cut type).

Ingredients		Content per ampule (1 mL)
Active ingredient	Mecobalamin	500 μg
Inactive ingredient	D-Mannitol	50 mg
Product description		Methycobal is a clear, red liquid
pH		5.3 - 7.3
Osmotic pressure ratio		about 1 (ratio relative to isotonic sodium chloride solution)

INDICATIONS

Peripheral neuropathies

Megaloblastic anemia caused by vitamin B_{12} deficiency

<Precautions>

METHYCOBAL should not be used aimlessly for more than one month unless it is effective.

DOSAGE AND ADMINISTRATION

- **Peripheral neurophathies**

  The usual dosage for adults is 1 ampule (500 μg of mecobalamin) daily, administered intramuscularly or intravenously 3 times a week. The dosage may be adjusted depending on the patient's age and symptoms.

- **Megaloblastic anemia**

  The usual dosage for adults is 1 ampule (500 μg of mecobalamin) daily, administered intramuscularly or intravenously 3 times a week. After about 2 months of medication, the dose should be reduced to a single administration of 1 ampule at 1 to 3 months intervals for maintenance therapy.

PRECAUTIONS

1. Adverse Reactions

   Adverse reactions were reported in 13 of 2,872 patients (0.45 %). (At the end of the reexamination period)

   (1) Clinically significant adverse reactions (incidence unknown)

   Anaphylactoid reaction

   Anaphylactoid reaction such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

   (2) Other adverse reactions

	<0.1%	Incidence unknown
Hypersensitivity (skin)	Rash	
Others	Headache and hot sensation	Diaphoresis and pain/induration at the site of intramuscular injection

   Note: In the event of such symptoms, treatment should be discontinued.

2. **Precautions concerning Use**

   (1) Administration

   METHYCOBAL is susceptible to photolysis. It should be used promptly after the package is opened, and caution should be taken so as not to expose the ampules to direct light.

   (2) Intramuscular administration

   In intramuscular administration, caution should be exercised by following the instructions mentioned below to avoid adverse effects on tissues or nerves.

   1) Avoid repeated injection at the same site. Particular caution should be exercised when administering METHYCOBAL to prematures, neonates, nursing infants and children.

   2) Do not inject in densely innervated site

   3) If insertion of the injection needle causes intense pain or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.

(3) Opening the ampule

METHYCOBAL is supplied in one-point-cut ampules. The cut point of the ampules should be wiped with an alcohol swab before opening.

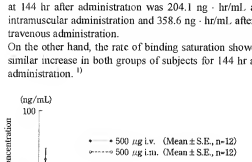
PHARMACOKINETICS

1. **Single-dose administration**

Mecobalamin was administered intramuscularly or intravenously to 12 healthy adult male volunteers at a single dose of 500 μg. The time to reach peak serum total vitamin B_{12} (abbreviated to B_{12}) concentration (t_{max}) was 0.9 hr after intramuscular administration and immediately to 3 min after intravenous administration, and the increment (except endogenous serum total B_{12}) in peak serum total vitamin B_{12} concentration (ΔC_{max}) was 22.4 ng/mL after intramuscular administration and 85.0 ng/mL after intravenous administration.

The area under the serum total B_{12} concentration-time curve (ΔAUC) calculated by increment of the actual values at 144 hr after administration was 204.1 ng · hr/mL after intramuscular administration and 358.6 ng · hr/mL after intravenous administration.

On the other hand, the rate of binding saturation showed a similar increase in both groups of subjects for 144 hr after administration. [1]



Serum total vitamin B_{12} concentration after single administration of METHYCOBAL Injection 500 μg

Pharmacokinetic parameters after a single dose administration of Methycobal Injection 500 μg

	t_{max}(hr)	ΔC_{max}(ng/mL)	ΔAUC_0^{144}(ng·hr/mL)	$t_{1/2}$ (hr)
I.V	0- 5 min	85.0±8.9	358.6±34.4	27.1
I.M	0.9±0.1	22.4±1.1	204.1±12.9	29.0

Mean ± S.E., n=12

2. **Repeated-dose administration**

Mecobalamin was administered intravenously to 6 healthy adult male volunteers at a single dose of 500 μg daily for 10 consecutive days. Serum total B_{12} concentration determined before each administration increased from day to day. After 2 days of administration, the serum total B_{12} concentration was 5.3±1.8 ng/mL, about 1.4 times the 24 hr value (3.9±1.2 ng/mL) after administration. At 3 days of administration it had increased to 6.8±1.5 ng/mL, about 1.7 times the 24 hr value, and this concentration was maintained until the last dosing. [1]

CLINICAL STUDIES

Clinical efficacy

Mecobalamin was administered intramuscularly to patients with peripheral neuropathies at a single doses of 500 μg and 100 μg (low-dose group) daily 3 times a week for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage of peripheral neuropathies in the 500 μg group aggravation of symptoms was significantly suppressed compared to the low-dose group and this dose was thus demonstrated to be useful. [2]

In a placebo-controlled double-blind clinical trial, mecobalamin was administered intravenously or intramuscularly to patients with peripheral neuropathies at a single dose of 500 μg daily 3 times a week for 4 consecutive weeks. The improvement rate for intravenous administration was 38.7% (24/62) for moderately to remarkably improved and 74.2% (46/62) for fairly to remarkably improved. The improvement rate for intramuscular administration was 46.3% (25/54) for moderately to remarkably improved and 81.5% (44/54) for fairly to remarkably improved. The equivalence of mecobalamin efficacy for both administration routes was thus demonstrated. The diseases of subjects in the trial were diabetic neuropathy, polyneuritis, cervical spondylosis, sciatica, alcoholic neuropathy, facial paralysis and mononeuritis, etc. [3]

When mecobalamin was administered to patients with megaloblastic anemia due to vitamin B_{12} deficiency, their hemograms and symptoms improved in 3 weeks to 2 months after starting administration.

PHARMACOLOGY

1. **Mecobalamin is a kind of endogenous coenzyme B_{12}**

Mecobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine.

2. **Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis.**

Mecobalamin is better transported to nerve cell organelles than cyanocobalamin in rats. It has been shown in experiments with cells from the brain origin and spinal nerve cells in rats to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid. Also, mecobalamin promotes nucleic acid and protein synthesis in rats more than cobamamide does. [4-6]

3. **Mecobalamin promotes axonal transport and axonal regeneration.**

Mecobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine (in rats and rabbits), models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus. [7-12]

4. **Mecobalamin promotes myelination (phospholipid synthesis).**

Mecobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipid and increases myelination of neurons in rat tissue culture more than cobamamide does. [13,14]

5. **Mecobalamin restores delayed synaptic transmission and diminished neurotransmitters to normal.**
Mecobalamin restores end-plate potential induction early by increasing nerve fiber excitability in the crushed sciatic nerve in rats. In addition, mecobalamin normalizes diminished brain tissue levels of acetylcholine in rats fed a choline-deficient diet. [15, 16]

6. **Mecobalamin promotes the maturation and division of erythroblasts, thereby alleviating anemia.**
It is well known that vitamin B_{12}-deficiency may cause specific megaloblastic anemia. Mecobalamin promotes nucleic acid synthesis in bone marrow and promotes the maturation and division of erythroblasts, thereby increasing erythrocyte production. Mecobalamin brings about a rapid recovery of diminished red blood cell, hemoglobin, and hematocrit in vitamin B_{12}-deficient rats.

PHYSICOCHEMISTRY

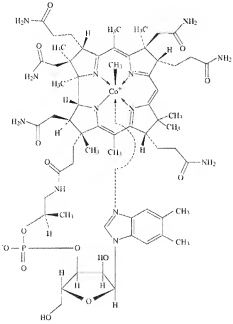
Nonproprietary name: Mecobalamin (JAN, INN)

Chemical name:
Co α-[α-(5,6-Dimethylbenz-1*H*-imidazolyl)]-Coβ-methylcobamide

Molecular formula: $C_{63}H_{91}CoN_{13}O_{14}P$

Molecular weight: 1,344.38

Structural formula:



Description:
Mecobalamin occurs as dark red crystals or crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (99.5), and practically insoluble in acetonitrile.
It is affected by light.

PRECAUTION FOR HANDLING

METHYCOBAL is packaged in the LPE pack (Light Protect Easy open pack) to ensure quality during storage.
The LPE pack should be opened immediately before using.

PACKAGING

METHYCOBAL Injection 500 μg (1mL)
Boxes of 10 and 50 ampules

REFERENCES

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2) Kameyama M. et al.: Jpn. J. Clin. Exp. Med., **49,** 1967, 1972.
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4) Inada M. et al.: Nervous systems and Methyl B_{12} (Kyowa kikaku tsuushin), **23,** 1981.
5) Nakazawa T. et al.: Vitamin, **42,** 193, 1970.
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8) Ohnishi A. et al.: Jpn. J. Clin. Pharmacol. Ther., **18,** 387, 1987.
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13) Nakagawa T. et al.: Nervous Systems and Methyl B_{12} (Kyowa kikaku tsuushin), 54, 1981.
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15) Shibuya T. et al.: *ibid.*, 134, 1981.
16) Sasaki H. et al.: Pharmacol. Biochem. Behav., **43,** 635,1992.

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Safety Management Department
Fax: 03-3811-2710
Eisai Co., Ltd.
5-5, Koishikawa 5-chome, Bunkyo-ku, Tokyo, 112-8088

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Customer Information Services Section
Free Dial: 0120-419-497
Eisai Co., Ltd.

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